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Original Research Article

Response Evaluation in Brain Metastasis with Whole Brain Radiotherapy and Temozolomide

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ABSTRACT

Background: Approximately 20%–40% of cancer patients develop brain metastases (BM). Whole-brain radiotherapy (WBRT) is the standard treatment for patients with brain metastases. Although WBRT can reduce neurologic symptoms, the median survival following WBRT is between 3 and 6 months. We have compared the clinical response and overall survival with WBRT alone and WBRT with concomitant Temozolomide (TMZ) in patients of brain metastases in this two arm study.

Methods: We have enrolled 40 patients, divided into two arms of 20 patients in each arm. First arm patients received only 30 Gy WBRT while second arm received 30 Gy WBRT with concomitant TMZ (75mg/m2/day).The primary end points were objective response rate (ORR), overall survival rate (OSR) and progression free survival rate (PFSR).

Results: In Arm-I, 3 patients had a complete response, 7 patients had a partial response and in Arm-II, 5 patients had a complete response, 9 patients had a partial response. The objective response rate was 50%in Arm-I and in Arm-II it was 70%. Overall survival rate was 60%in Arm-I and 70% in Arm-II. In Arm-I overall survival was 6.2 months while in Arm-II it was 7.4 months. The progression free survival was also better in Arm-II (45% vs. 35%). Deaths were more in the Arm-I (40% vs. 30%).

Conclusion: Combination of WBRT and TMZ has better clinical response in patients with brain metastases. It improves ORR, OSR, & PFSR.

Keywords: Brain Metastasis, Temozolomide, Whole Brain Radiotherapy.

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INTRODUCTION

Brain metastasis is the most common intracranial tumor, occurring in approximately 20% to 40% of adult patients with cancer[1]. The incidence of these metastases has increased in recent years and they are associated with poor prognosis despite of aggressive treatment. The median survival time of untreated patients is approximately 1 month[2].

The risk of developing brain metastasis varies according to primary tumor type. The most common primary cancers that metastasize to the brain are lung, breast, and gastrointestinal cancers. Approximately half of the brain metastases occur due to lung cancer[2].

Patients may complaint nausea, vomiting, headaches, focal weakness, mental disturbances, behavioural changes, seizures, speech difficulty, and ataxia. They may have severe neurologic symptoms with a decrease in survival and quality of life[3].

About 30%–40% of affected patients present with a single brain metastasis, but most present with multiple lesions[4]. Patients with a single brain metastasis benefit from surgery or radiosurgery. However, single metastases are rare and WBRT remains the standard treatment for most[5].

Frequently the palliative approaches focused on symptomatic care remain the standard treatment to relieve neurologic symptoms, primarily with the use of corticosteroids, osmotic diuretics and anti-convulsant. The objective of WBRT is to provide symptomatic relief, to allow for tapering of the dose of corticosteroids, and to possibly improve survival. WBRT improves specific neurologic symptoms in the majority of patients, but response duration is short and the treatment may be associated with late complications[6].

Available treatment options are limited, as many chemotherapeutic agents do not penetrate the blood-brain barrier[7].

Temozolomide (TMZ) is an oral imidazotetrazinone methylating agent[8]. TMZ is rapidly absorbed and converted to Monoethyl Triazenoimidazole Carboxamide (MTIC) which causes methylation of the O^6 position of guanine[9].

After oral administration TMZ is highly bio-available and has excellent central nervous system penetration[10]. The common side effects are nausea and vomiting. Primary toxicity associated with TMZ is the Myelosuppression, but it is manageable in the majority of patients.

Phase III trials of the Radiation Therapy Oncology Group (RTOG) showed that treatment of brain metastasis with WBRT results in a median survival of 4 to 6 months and improve the neurologic function in most patients. The concomitant use of TMZ and WBRT is well tolerated and there is significantly higher response rate[11].

The primary aim of this study was to compare the objective response rate of WBRT alone and the combination of WBRT and TMZ in patients with previously untreated BM from solid tumours. We also evaluated the overall survival, progression free survival, safety and tolerability.

OBJECTIVES

Primary

- To compare the objective response rate in patients with BM treated with WBRT alone vs. WBRT and concomitant TMZ.

Secondary

- To compare overall survival.
- To compare local progression-free survival.

MATERIALS AND METHODS

This was a randomised prospective comparative study. Between October 2012 and September 2013, 40 patients completed RT and were assessable for the study. The Institutional Ethics Committee approval was taken and informed consent was received before beginning the treatment.

Eligibility Criteria

- Radio-logically proved brain metastases
- ECOG performance status 2-4
- Liver transaminases ≤ 1.5 times upper limit of normal (ULN)
- Creatinine < 1.5 times ULN
- No other serious concurrent disease
- No contraindications to treatment with Temozolomide
- At least 10 days since prior chemotherapy

Study design

The 40 patients were divided in 2 arms, 20 in each arm.

Arm-I: Patients received radiotherapy to the brain 5 times a week for 2 weeks.

Arm-II: Patients undergo radiotherapy as in Arm-I and receive oral Temozolomide once daily for 2 weeks.

Treatment schedule

Conventional WBRT was given as daily dose of 3 Gy for 5 days a week for two weeks to a total dose of 30 Gy. TMZ was administrated orally as a dose of 75 mg/m^2/day 1hour before the radiation treatment. Patients received corticosteroids at the lowest dose necessary to maintain neurologic stability, and anti-convulsants were given when indicated.

Patient evaluation

All patients underwent baseline complete clinical evaluation before treatment.

Target lesions were assessed by computed tomography (CT) or gadolinium-enhanced magnetic resonance imaging (Gd-MRI) before the onset of treatment.

Radiologic evaluation of target lesions was performed at 6 weeks according to the RECIST criteria as described below[12].

- Complete response (CR): Disappearance of all known brain metastases.
- Partial response (PR): 50% or greater decrease in measurable brain lesions or an objective improvement in evaluable brain lesions.
- Stable disease (SD): Brain lesions unchanged (< 50% decrease or < 25% increase in the size of measurable lesions).
- Progressive disease (PD): >25% increase in size of some or all of brain lesions and/or the appearance of any new brain lesions.

Statistical analysis

The statistical significance of the differences in survival distribution among the prognostic groups was evaluated by the log-rank test. A univariate analysis for each prognostic variable on overall survival and progression free survival was estimated according to the Kaplan-Meier method[13]. Factors reaching significance of univariate analysis were entered in a multivariate analysis using the Cox stepwise logistic regression test to investigate the independence of the various risk factors. P-values <0.05 was regarded as statistically significant in two tailed tests. SPSS software (version 10.00, SPSS, Chicago) was used for statistical analysis.

Table 1: Patients characteristics

Characteristics		Arm-I	Arm-II
Age (y)	**≥65**	8	9
	<65	12	11
Gender	**Male**	13	12
	Female	7	8
Primary tumour	**Lung**	7	9
	Breast	8	6
	Other	6	4
ECOG status	**2**	7	6
	3	8	8
	4	5	6
Previous chemotherapy	**Yes**	14	12
	No	06	08

Table 2: Brain Lesion Response to Treatment

Response	Arm-I		Arm-II	
	No.	**%**	**No.**	**%**
Complete Response	3	15	5	25
Partial Response	7	35	9	45
Objective Response	10	50	14	70
Stable Disease	5	25	4	20
Progressive Disease	5	25	2	10

Table 3: Survival Status at the end of 6 months

Status at the end of 6 months	Arm-I		Arm-II	
	No of pts.	%	No of pts.	%
Alive	12	60	14	70
Dead	08	40	06	30

Table 4: Overall Response to Treatment

Overall Response	Arm-I	Arm-II
Overall survival rate	60%	70%
Progression free survival rate	35%	45%

RESULTS

The demographics and baseline disease characteristics of the assessable patients are listed in Table 1. Among 40 assessable patients 16 (40%) had non-small cell lung cancer, 14 (35%) had breast cancer and 10 (25%) had other cancers (colo-rectal carcinomas, melanoma, ovarian cancer and testicular cancer). The majority of patients, 26 out 40, had received chemotherapy for primary cancer before entering the study. Patients were comparable in both the arms according to all of the parameters.

All of the patients were radiologically evaluated after treatment. Radiologic evaluation of target lesions was performed at 6 weeks according to the RECIST criteria. The response is shown in Table 2. The CR was observed in 3 patients in Arm-I and 5 patients in Arm-II while PR was seen in 7 patients in Arm-I and 9 patients in Arm-II. The objective response (CR+PR) was observed in 10 patients in Arm-I and 14 patients in Arm-II. Data reveals 70% objective response rate in Arm-I and 60% in Arm-II. The p-value of OR is 0.197, which is statistically not significant. Stable disease was achieved in 5 patients in Arm-I and 4 patients in Arm-II. The disease was progressive in 5 patients in Arm-I and 2 patients in Arm-II.

The overall survival rate was 60% in Arm-I as compared to 70% in Arm-II. The median survival was 9.2 months in Arm-I while 11.4 months in Arm-II. The p-value for overall survival rate is 0.507.

The progression-free survival was 4.6 months in Arm-I while 7.5 months in Arm-II. The progression-free survival rate was 35% in Arm-I while 45% in Arm-II.The p-value for progression-free survival rate is 0.514.

DISCUSSION

Previous studies Addeo R. et. al. & Chua D. et. al. demonstrated that TMZ is well-tolerated and with better objective response rate. It shows significant improvement in quality of life, but without significant improvement in survival[14,15].

In our study we compared concurrent treatment with WBRT alone. Our data reveals 70% objective response rate (CR+PR) and 25% CR rate with concurrent Tt. There was slight improvement in OSR (70%) as compared to WBRT alone (60%). Better median survival of 11.4 months was seen in concurrent Tt arm. PFSR of 45% was also encouraging.

Responses were independent from the type of primary tumor, gender and previous chemotherapy. TMZ was well tolerated in this study. The addition of daily TMZ to WBRT resulted in only one grade-4 hematologic toxicity. Complications resolved quickly and resulted in minor treatment delay.

CONCLUSION

We have concluded that WBRT with concomitant TMZ is well tolerated, with better clinical response. It improves objective response rate, Overall Survival Rate, and Progression Free Survival rate.

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